54

ORIGINAL

Amendment to Pending Application
Safety Update

April 12, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism & Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation 11
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 13 1999
HFD-510

Novo Nordisk
Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: NDA 21-028
Velosulin BR® Human Buffered Regular Human Insulin Injection (rDNA origin)

Dear Dr. Sobel:

Reference is made to NDA 21-028 for Velosulin BR® (rDNA origin). Reference is also made to an April 7, 1999 telephone conversation between the Division and Novo Nordisk requesting a Safety Update for Velosulin BR® (rDNA origin) in connection with the review of the NDA.

There is no new safety information to update the pending NDA at this time.

If you have any questions regarding this submission, please contact Michael Barbush, Regulatory Affairs, at (609) 987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

BR/mibh

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
4-28-99
DATE
/S/

/S/
4/12/99

/S/
4/28/99

/S/
4/27/99

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 16, 1999

FROM: Mathematical Statistician, Team Leader, Div. of Biometrics 2 (HFD-715)

SUBJECT: Statistical review of Velosulin

TO: File (NDA 21-028)

The purpose of this memorandum is to clarify statements in the Conclusion Section of the statistical review. In particular, the statement "these data do not provide convincing statistical evidence of the equal efficacy of rDNA and semi-synthetic insulin" should be interpreted to mean that the data do not support nor contradict the equal efficacy of the two drug products. This observational study was not intended to serve as the basis of approval by FDA.

/S/ [redacted]

J. Todd Sahlroot, Ph.D.

Concur: Dr. Nevius /S/ [redacted] 7/17/99

Cc:
Orig. NDA 21-028
HFD-510/division file, SSobel, SMalozowski, Rmisbin
HFD-510/EGalliers, JRhee
HFD-715/division file, ENevius, TSahlroot

APPEARS THIS WAY ON ORIGINAL

MEMORANDUM

DATE: June 25, 1999

/S/ 6/28/99

FROM: Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: NDA 21-028 Velosulin BR (rDNA origin) Package Insert

TO: NDA 21-028 file

The pending NDA 21-028 Velosulin BR (rDNA origin) injection is a similar product as currently available Velosulin BR (semi-synthetic) injection (NDA 19-450), which was approved on May 30, 1986. The difference between these two insulin products is the method of manufacture. The NDA 19-450 is a semi-synthetic buffered regular insulin and the NDA 21-028 is a rDNA buffered regular insulin.

The package insert of currently available Velosulin BR (semi-synthetic) states that Velosulin BR (semi-synthetic) has been tested only in (b)(4) C/C pumps, using the accompanying . as well as both APPEARS THIS WAY ON ORIGINAL . infusion sets. The package insert also states that . pumps are equivalent.

According to the CDRH, when insulin external pumps get their 510(k) clearance, the pump is not cleared with specific insulin(s) to be used with the pump.

However, since the drug product in this NDA, which is a drug/device combination, was tested with MiniMed® pump alone, we cannot request the sponsor of the NDA to include other external pumps on the package insert without any supporting data.

Attachment: Copy of the 6/8/99 e-mail from Ms. Kim Dettelbach, General Counsel.

cc: Orig NDA
HFD-510/Div File

APPEARS THIS WAY ON ORIGINAL

21-cc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-028

JUL 31 1998

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President
100 Overlook Center, Suite 200
Princeton, NJ 98540-7810

Dear Dr. Reit:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Velosulin BR [insulin human injection (rDNA origin)]

Therapeutic Classification: Standard (S)

Date of Application: July 22, 1998

Date of Receipt: July 23, 1998

Our Reference Number: NDA 21-028

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 21, 1998, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 23, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

If you have any questions, contact Julie Rhee, Regulatory Health Project Manager, at (301) 827-6424.

Sincerely yours,

/S/ [redacted]

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

AMENDMENT TO NDA #21-028

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

July 1, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-028 Velosulin BR® Human Buffered Regular Human Insulin Injection (rDNA origin)

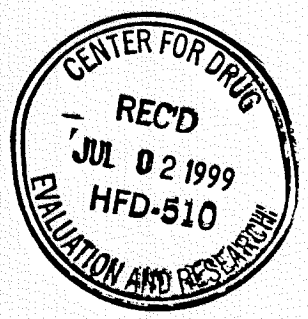
Dear Dr. Sobel:

Please refer to our New Drug Application 21-028 for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA origin), which was submitted on July 22, 1998. Reference is also made to the following communications: (1) a June 23, 1999 electronic mail message from Julie Rhee, Project Manager, to Novo Nordisk to which was attached a copy of the draft patient package insert for Velosulin BR® (rDNA origin) product containing the Division's comments; (2) a June 30, 1999 electronic mail message from Novo Nordisk to Julie Rhee containing our responses to the Division's comments on the June 23 draft patient package insert; and (3) two July 1, 1999 telephone conversations between Julie Rhee and Novo Nordisk to discuss the Division's rejoinder to Novo Nordisk's comments and a final resolution of all comments on the draft patient package insert for Velosulin BR® (rDNA origin) product. Ms. Rhee also requested that the draft package insert be revised based on the mutually agreed upon comments and submit this document via an electronic mail message to her atention and as an official amendment to the pending NDA.

In response to this last mentioned request, Novo Nordisk is amending NDA# 21-028 to provide the most current revised draft patient package insert for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA origin).

Any questions or comments regarding this submission should be directed to Michael Barbush, Regulatory Affairs, at 609/987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.



Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosures

DUPLICATE BL

AMENDMENT TO NDA #21-028

June 15, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: NDA 21-028 Velosulin BR® Human Buffered Regular Human Insulin Injection (rDNA origin)

Dear Dr. Sobel:

Please refer to our New Drug Application 21-028 for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA origin), which was submitted on July 22, 1998. Reference is also made to the following communications: (1) a May 4, 1999 electronic mail message from Julie Rhee, Project Manager, to Novo Nordisk to which was attached a copy of the revised draft patient package insert for Velosulin BR® (rDNA origin) product containing comments made by CDRH-FDA, and (2) a June 11, 1999 telephone conversation between Julie Rhee and Novo Nordisk requesting that we submit our responses to CDRH's comments and provide a sanitized version of the current draft patient package insert for Velosulin BR® (rDNA origin) as an official amendment to the pending NDA.

In response to this last mentioned request, Novo Nordisk is amending NDA# 21-028 to inform the Division that we are in agreement with the comments made by CDRH and are providing a sanitized version of the draft patient package insert for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA origin).

Any questions or comments regarding this submission should be directed to Michael Barbush, Regulatory Affairs, at 609/987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.

Barry Ret, Ph.D.
Vice President, Regulatory Affairs

Enclosures
cc: Ms. Julie Rhee

Desk Copy

Response to FDA Request for Information

Novo Nordisk

February 24, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 21-028 Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA)

Dear Dr. Sobel:

Please refer to our New Drug Application 21-028 for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA), which was submitted on July 22, 1998. Reference is also made to a February 23, 1999 telephone conversation between Ms. Julie Rhee, Project Manager, and Novo Nordisk asking Novo Nordisk to submit a side-by side comparison of the currently approved patient package insert for Velosulin BR Human, Buffered Regular Human Insulin Injection (semi-synthetic) with the draft patient package insert for Velosulin BR Human, Buffered Regular Human Insulin Injection (rDNA origin), with all differences annotated and explained.

In response to this query, enclosed please find a side-by side comparison of the currently approved patient package insert for Velosulin BR Human, Buffered Regular Human Insulin Injection (semi-synthetic) with the draft patient package insert for Velosulin BR Human, Buffered Regular Human Insulin Injection (rDNA origin), with all differences annotated and explained following the side-by-side comparison. Two(2) official copies and one (1) desk copy of the requested information are provided in this response.

We trust that you will find this information helpful in your evaluation and review of the application. If you have any questions, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973 (phone) or 609-987-3916 (fax).

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

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ORIGINAL

NDA Amendment

ORIG AMENDMENT

BT

December 23, 1998

Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 21-028 Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA)
NDA Amendment: Response to Microbiology Review Comments

Dear Dr. Sobel:

Please refer to our New Drug Application 21-028 for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA), which was submitted on July 22, 1998. Reference is also made to your December 3, 1998 facsimile containing comments generated during the review of the microbiology section of the NDA.

In response to this review we are submitting, in duplicate, an amendment to NDA 21-028 regarding the sterilizing filtration of the bulk product solution ([redacted] Validation Report, Section IV.B). Pursuant to 21 CFR 314.60 (c), we are providing a field copy to the FDA district office as the sterilization package was also submitted in the Chemistry, Manufacturing and Controls section of the NDA.

The amendment is composed of Enclosure A (Response to Question 1a: [redacted] specification for bulk solution) and Enclosure B (Response to Question 1b: Further descriptions of the [redacted] validation of the [redacted] additional data from the validation studies including the [redacted] integrity test results).

For ease of review we have enclosed a copy of the December 3, 1998 facsimile and an introductory summary of the amendment.

We trust that you will find this information helpful in your evaluation and review of the application. If you have any questions, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973 (phone) or 609-987-3916 (fax).

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: FDA District Office (Field Copy Certification)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

/s/ [redacted] 3-19-99
CSO INITIALS DATE

Micro review completed 1-29-99.

DUPLICATE

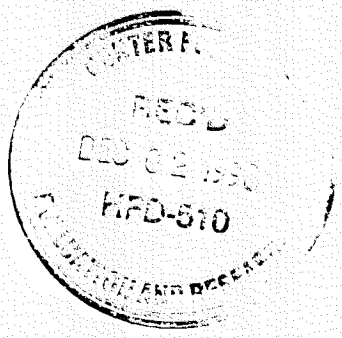
ORIG AMENDMENT

BC

Response to FDA Request for Information

December 1, 1998

Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 21-028 Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA)

Dear Dr. Sobel:

Please refer to our New Drug Application 21-028 for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA), which was submitted on July 22, 1998. Reference is also made to a November 24, 1998 telephone conversation between William Berlin, Ph.D., Chemistry Reviewer, and Novo Nordisk to request clarification on the sameness of the manufacturing process equipment used to manufacture both the approved Velosulin BR semi-synthetic product and the pending rDNA product.

In response to this request, please note that the process equipment (i.e., solution filtration, filling line, aseptic assembly, etc.) used to manufacture the Velosulin BR semi-synthetic product and the rDNA product is the same. This is described in the [redacted] Process Validation Reports contained in the following reports:

- Annual Report dated 01-Apr-1998: Documentation for [redacted] Process Validation: Regular Purified Insulin 100 U/ml, 10 ml and Velosulin® BR Buffered Regular Human Insulin Injection (semi-synthetic) 100 U/ml, 10 ml, and
- Report 01-Jun-1998: Documentation for [redacted] Process Validation: Velosulin® BR Buffered Regular Human Insulin Injection (rDNA) 100 U/ml.

Specific information is found in the following sections of the reports:

Section IV.A: The compounding and aseptic filling of the two preparations takes place in the same rooms in building [redacted] utilizing the same process equipment, such as [redacted]

Section IV.B: The [redacted] used for [redacted] of the drug products, and the [redacted] periods are the same for the two preparations.

Section IV.C: The validation of the [redacted] processes for containers, closures, equipment and components is identical for the two preparations.

Section IV.D & IV.E: Results from the same [redacted] are reported in the two reports. The procedures enclosed / reported in these sections are updated and written in a more appropriate form between the two reports, but the [redacted] are still the same.

We trust that you will find this information helpful in your evaluation and review of the application. If you have any questions, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973 (phone) or 609-987-3916 (fax).

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

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APPEARS THIS WAY ON ORIGINAL

[redacted]

AMENDMENT TO NDA #21-028

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

April 26, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-028 Velosulin BR® Human Buffered Regular Human Insulin Injection (rDNA origin)

Dear Dr. Sobel:

Please refer to our New Drug Application 21-028 for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA origin), which was submitted on July 22, 1998. Reference is also made to the following communications: (1) a March 25, 1999 electronic mail message from Julie Rhee, Project Manager, to Novo Nordisk to which was attached a copy of the draft patient package insert for Velosulin BR® (rDNA origin) product containing the Division's comments; (2) an April 6, 1999 electronic mail message from Novo Nordisk to Julie Rhee containing our responses to the Division's comments on the draft patient package insert; and (3) an April 26, 1999 telephone conversation between Julie Rhee and Novo Nordisk requesting that the April 6, 1999 communication be regarded as an official amendment to the pending NDA and asking us to submit only the revised draft patient package insert from the April 6 electronic mail message.

In response to this last mentioned request, Novo Nordisk is amending NDA# 21-028 to provide the revised draft patient package insert for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA origin).

Any questions or comments regarding this submission should be directed to Michael Barbush, Regulatory Affairs, at 609/987-5973.

Sincerely,
Novo Nordisk Pharmaceuticals, Inc.

APPEARS THIS WAY ON ORIGINAL

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosures
cc: Ms. Julie Rhee

Desk Copy

Response to FDA Request for Information

February 24, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 21-028 Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA)

Dear Dr. Sobel:

Please refer to our New Drug Application 21-028 for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA), which was submitted on July 22, 1998. Reference is also made to a February 23, 1999 telephone conversation between Ms. Julie Rhee, Project Manager, and Novo Nordisk asking Novo Nordisk to submit a side-by side comparison of the currently approved patient package insert for Velosulin BR Human, Buffered Regular Human Insulin Injection (semi-synthetic) with the draft patient package insert for Velosulin BR Human, Buffered Regular Human Insulin Injection (rDNA origin), with all differences annotated and explained.

In response to this query, enclosed please find a side-by side comparison of the currently approved patient package insert for Velosulin BR Human, Buffered Regular Human Insulin Injection (semi-synthetic) with the draft patient package insert for Velosulin BR Human, Buffered Regular Human Insulin Injection (rDNA origin), with all differences annotated and explained following the side-by-side comparison. Two(2) official copies and one (1) desk copy of the requested information are provided in this response.

We trust that you will find this information helpful in your evaluation and review of the application. If you have any questions, please contact Michael Barbush, Regulatory Affairs, at 609-987-5973 (phone) or 609-987-3916 (fax).

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

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ORIGINAL

THIS IS NOT A SUBMISSION
Response to FDA Request for Information

Novo Nordisk

BM

November 10, 1998

Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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AND RESEARCH

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-987-3916

RE: NDA 21-028 Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA)

Dear Dr. Sobel:

Please refer to our New Drug Application 21-028 for Velosulin® BR Human, Buffered Regular Human Insulin Injection (rDNA), which was submitted on July 22, 1998. Reference is also made to several telephone conversations between Robert Misbin, M.D., Medical Reviewer, and Novo Nordisk, the most recent being held on November 9, 1998, to request the following: (1) clarification on the use of different units used to express the fructosamine concentrations in certain tables contained in the Clinical Trial Report [redacted]/009/USA, and (2) the normal fructosamine values for the assay .

In our October 20th response to Dr. Misbin's inquiry, we indicated that the correct units to define the fructosamine levels throughout the study report are "µmol/L". The units appearing in Table 6.1 were a typographical error and should have been "µmol/L", which conforms to the "End of Text" table (Table 1) for Table 6.1, which had the units in "µmol/L" for the fructosamine levels. A revision of Table 6.1 is attached for your review.

Also provided in this response is a copy of the [redacted] method used by [redacted] in Clinical Trial Report [redacted]/009/USA). The method provides the reportable and normal ranges for the assay, along with the [redacted]. The concentration units for these assay parameters are in "µmol/L."

We trust that this information will be helpful in the Division's evaluation and review of Clinical Trial Report [redacted]/009/USA, and we apologize for our delays in supplying Dr. Misbin with this information. If you have any questions, please contact the undersigned at 609-987-5973 (phone) or 609-987-3916 (fax).

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

MAF

/S/ [redacted]
11/13/98

Michael Barbush
Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ [redacted] 11-30-98
DATE

/S/ [redacted]
11/30/98

BEST POSSIBLE COPY

Table 6-1: Summary of Patient's Characteristics

No. Treated	semi synthetic → rDNA 10	rDNA → semi synthetic 10
Age (yrs)		
Mean (SD)	35.3 (9.60)	37.3 (11.61)
Min - Max	24 - 55	25 - 52
Race (%)		
Caucasian	100.0	100.0
Weight (kg)		
Mean (SD)	82.5 (9.38)	87.8 (9.24)
Min - Max	72 - 103	75 - 102
Height (cm)		
Mean (SD)	176.1 (5.91)	178.6 (7.31)
Min - Max	169 - 186	168 - 191
BMI (kg/m^2)		
Mean (SD)	26.6 (2.39)	27.5 (1.26)
Min - Max	23 - 30	26 - 30
Fructosamine (µmol/L)		
Mean (SD)	331.0 (35.90)	373.5 (37.65)
Min - Max	259 - 365	333 - 450
Hemoglobin A_{1c} (%)		
Mean (SD)	7.4 (0.71)	7.9 (0.75)
Min - Max	5.8 - 8.2	6.7 - 8.9

Data from End-of-Text Table I

Medical History

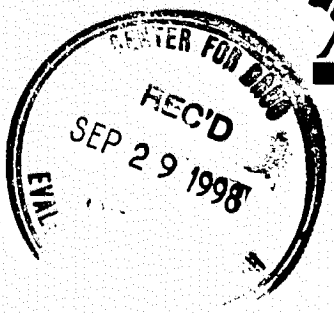
Patients had medical histories of various diseases common for a population with type I diabetes. A history of disease/condition with a sub-category indicting whether the condition was active or not is listed in End-of-text Table 2 and CRF Tabulations 5 and 5.1.

None of the conditions were considered by the investigator to interfere with the inclusion of patients in the study.

GENERAL CORRESPONDENCE
REQUEST FOR INFORMATION

Novo Nordisk

September 28, 1998



Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: NDA 21-028 Velosulin BR® Human Buffered Regular Human Insulin Injection (recombinant DNA origin) - Supplement 001

Dear Dr. Sobel:

In response to your facsimile dated August 14, 1998 (copy attached), which consisted of a request from Dr. Hae-Young Ahn, Biopharm Team Leader, DMEDP, for additional information in connection with the review of NDA # 21-028 for Velosulin BR® Human Buffered Regular Human Insulin Injection (recombinant DNA origin), enclosed please find two (2) diskettes which provide the following information:

- Diskette A contains the Study Synopsis for Study INS/USA/008/USA in WORD® format (filename "study synopsis") and Individual standard curves and QC samples for all analytical runs for Study [redacted]/008/USA in EXCEL® format (filenames "Ins008us" and "Ins008us-glucose"); and
- Diskette B contains Individual PK/PD data from Study [redacted]/008/USA in EXCEL® format (filename "Ins008_pkpd").

We trust that this information will satisfy the Biopharm reviewer's request. Any questions or comments regarding this submission should be directed to Michael Barbush, Regulatory Affairs, at 609/987-5973.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

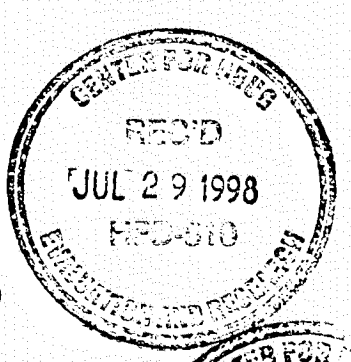
Enclosures

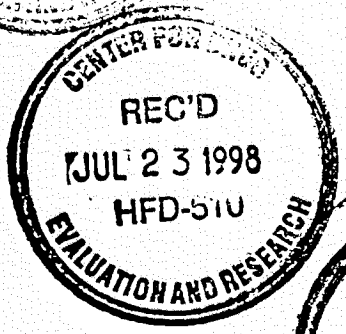
cc: Ms. Julie Rhee

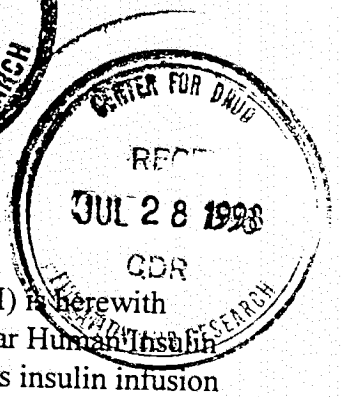
ORIGINAL NEW DRUG APPLICATION

Novo Nordisk

July 22, 1998







Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

Re: NDA N021028

Dear Dr. Sobel:

Pursuant to 21 CFR 314.50, Novo Nordisk Pharmaceuticals, Inc. (NNPI) is herewith submitting an original NDA for Velosulin BR® Human Buffered Regular Human Insulin Injection (recombinant DNA origin), for use in continuous subcutaneous insulin infusion therapy for diabetes mellitus.

Efficacy and safety data for the drug substance (recombinant DNA origin insulin) have been previously submitted in NDA No. 19-938 for Novolin® R, Regular, Human Insulin Injection (recombinant DNA origin) USP, [filed July 11, 1989] and IND No [redacted] for Novolin® R, Regular, Human Insulin Injection (recombinant DNA origin) USP, [redacted] and are incorporated by reference in this submission. Two studies with the subject drug product, a bioequivalence study and a comparative efficacy study with the current buffered regular human semi-synthetic insulin, are provided with the subject application.

This NDA contains nine volumes. The Nonclinical Pharmacology and Toxicology section data are provided in NDA No. 19-938 as referenced above. It was also agreed upon with the Agency prior to this submission, that an Integrated Summary of Safety and of Efficacy would not be necessary since only two studies are being submitted, and summaries for each of the studies would be included in their respective sections. Additionally, the case report tabulations and case report forms associated with the studies are presented in the appendices of the final reports only. The statistical presentation and analyses usually presented in Section 10 are limited to those presented in sections 6 and 8 as part of the study reports.

This application is being filed in duplicate (FDA archive copy and technical review copies). For each technical review section, a copy of Volume 1 of the NDA is provided. This volume contains various administrative documents, the NDA Index and the Application Summary. Novo Nordisk Pharmaceuticals Inc. is also providing directly to the Division the field copy of the Item 3, Chemistry, Manufacturing and Controls section. A certification for the Field Copy appears in Volume 1 of the NDA.

Following this letter is FDA Form 356h and the User Fee Cover Sheet. The User Fee was wired to the Mellon Bank in Pittsburgh, PA [redacted] Confirmation of receipt was made via telephone to Michael Jones, 301-594-2041 on July 20, 1998.

Questions or comments regarding this application should be directed to Michael Barbush, Regulatory Affairs, at 609/987-5973.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL